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Original article

Leptin and adiponectin in patients with systemic lupus erythematosus: clinical and laboratory correlations

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ABSTRACT

Objective: To evaluate the serum levels of leptin and adiponectin in patients with systemic lupus erythematosus (SLE) and correlate their levels with disease activity, presence of autoantibodies and clinical manifestations.
Methods: 52 women with SLE and 33 healthy women were evaluated. The patients were divided into two groups, the first with active SLE and the second with inactive SLE. Patients with SLEDAI $\geq$3 were considered active. Serum levels of leptin (ng/mL) and adiponectin (μg/mL) were measured by enzyme immunoassay.
Results: There was a significant difference in leptin levels between SLE and controls (20.7 ± 17.1 vs. 8.0 ± 5.0 ng/mL, $p < 0.001$), but no significant difference in adiponectin levels ($87\ 5 \pm 69.7$ vs. 118.1 ± 70.6 pg/mL, $p = 0.053$). No significant difference in levels of leptin and adiponectin was noted between inactive and active SLE groups. There was a significant association between low levels of leptin and positivity for anticardiolipin (aCL) ($p = 0.025$) and lupus anticoagulant (LA) ($p = 0.003$) and a significant association between high levels of leptin and the presence of renal disease ($p < 0.001$). However, there was no association between adiponectin levels with autoantibodies and clinical features in SLE patients.
Conclusion: Patients with SLE had elevated leptin levels, with association with renal involvement. Leptin and adiponectin were not correlated with disease activity. Low levels of leptin have been associated with the presence of LA and aCL.

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Leptina e adiponectina no lúpus eritematoso sistêmico: correlações clínicas e laboratoriais

Palavras-chave:
Lúpus eritematoso sistêmico
Leptina
Adiponectina

RESUMO

Objetivo: Avaliar os níveis séricos de leptina e adiponectina em pacientes com lúpus eritematoso sistêmico (LES) e correlacionar seus níveis com atividade inflamatória, presença de autoanticorpos e manifestações clínicas.

Métodos: Foram avaliadas 52 mulheres com LES e 33 mulheres saudáveis. As pacientes foram divididas em dois grupos, o primeiro com LES ativo e o segundo com LES inativo. Foram consideradas em atividade as paciente com Sledai ≥ 3. Os níveis séricos de leptina (ng/mL) e adiponectina (ug/mL) foram medidos por ensaio imunoenzimático.

Resultados: Houve diferença significativa nos níveis de leptina entre LES e controle ($20{,}7 \pm 17{,}1$ vs. $8{,}0 \pm 5{,}0$ ng/mL, $p < 0{,}001$), mas não houve diferença significativa nos níveis de adiponectina ($87{,}5 \pm 69{,}7$ vs. $118{,}1 \pm 70{,}6$ ug/mL, $p = 0{,}053$). Entre LES inativo e ativo, não houve diferença significativa dos níveis de leptina e adiponectina. Houve uma associação significativa entre os baixos níveis de leptina e positividade para anticardiolipina (aCL) ($p = 0{,}025$) e anticoagulante lúpico (LA) ($p = 0{,}003$) e uma associação significativa entre níveis elevados de leptina e da presença de manifestação renal ($p < 0{,}001$). No entanto, não houve associação entre adiponectina com autoanticorpos e características clínicas nas pacientes.

Conclusão: Pacientes com LES apresentaram nível elevado de leptina, com associação ao envolvimento renal. A leptina e a adiponectina não se correlacionaram com a atividade da doença. Baixos níveis de leptina foram associados com a presença de LA e aCL.

Introduction

In recent years, a major route linking metabolism and the immune system has been described, after verification of an inflammatory state in obesity.[1] The adipose tissue is an organ that performs neuroendocrine and immune functions, producing various cytokines that include IL-6 and TNF-alpha, leptin, adiponectin and resistin, known as adipokines. These cytokines participate in a variety of physiological processes, such as food intake, insulin sensitivity, atherosclerosis, immunity and inflammation.[2] They represent a new group of proteins released from adipocytes, which act as modulators of the immune system.[3] Studies demonstrate the participation of these substances in rheumatic and inflammatory diseases.[4–7]

Leptin acts on the immune system as a proinflammatory cytokine. In animal models, its deficiency is associated with an increased susceptibility to infection and reducing the inflammation.[8] It promotes the proliferation and activation of T lymphocytes and induces production of Th1 cytokines.[1,9,10] Studies have reported increased leptin levels in systemic lupus erythematosus (SLE) patients.[11–13]

Adiponectin has anti-inflammatory action.[14] It inhibits the proliferation and activation of T lymphocytes, as well as lymphopoiesis and B lymphocytes.[15] High levels of adiponectin were found in patients with SLE,[12,16,17] although there is still controversy.

The aim of this study was to evaluate the levels of leptin and adiponectin in patients with SLE and its possible correlation with disease activity, presence of autoantibodies and clinical manifestations.

Patients and methods

52 female patients who met the American College of Rheumatology (ACR) classification criteria for SLE,[18] hospitalized and/or in outpatient care at the Rheumatology Department, Hospital das Clínicas, Medicine School, Universidade Federal de Goiás (HC/FM/UFG) were included.

The patients were divided into two subgroups: a subgroup of patients with active SLE ($n = 21$) and another subgroup of patients with inactive disease ($n = 31$). The control group comprised 33 healthy women matched for age. The exclusion criteria were: patients younger than 18 years old, pregnancy, history of myocardial infarction or diabetes, liver disease, renal failure, prednisone >20 mg/day and body mass index (BMI) >30 kg/m^2.

The study was approved by the Research Ethics Committee of the HC/UFG and all participants who agreed to participate signed an informed consent form.

The evaluation of patients included demographics, age at disease onset, disease duration, clinical manifestations and physical examination. At the time of evaluation, lipid profile, fasting glucose and tests of inflammatory activity were also obtained for each patient. Autoantibodies found in the clinical record were considered; for those patients for whom autoantibodies were not found, these were requested at the time of their inclusion in the study.

To obtain the profile of autoantibodies, ANA and anti-DNA were used; these tests were performed at the Immuno-Rheumatology Laboratory, HC/FM/UFG. ANA was obtained by indirect immunofluorescence on HEp-2 cells (Hemagen Diagnostics, Inc.) and anti-DNA by indirect immunofluorescence

Table 1 – Demographics, clinical and laboratory data of patients with SLE and controls.

Variables	SLE ($n=52$)	Control ($n=33$)	p
Age, years[a]	33.4 (±9.4)	32.5 (±10.5)	0.670
Disease duration, years[b]	7.5		
BMI, kg/m^2 [a]	23.8 (±3.5)	21.8 (±2.5)	0.008
Glucose, mg/dL[a]	76.2 (±9.9)	84.2 (±8.5)	<0.001
Total cholesterol, mg/dL[a]	178.1 (±41.7)	172.8 (±43.7)	0.575
HDL cholesterol, mg/dL[a]	50.6 (±15.9)	62.3 (±19.2)	0.003
LDL cholesterol, mg/dL[a]	98.2 (±26.4)	87.0 (±35.6)	0.102
Triglycerides, mg/dL[a]	140.3 (±94.0)	93.1 (±43.4)	0.008

SLE, systemic lupus erythematosus; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein.
[a] Data presented as mean (±standard deviation).
[b] Data presented as mean.

on *Crithidia lucillae*. A survey of antibodies to extractable nuclear antigens (ENA), anti-Ro, anti-La, anti-Sm and anti-RNP, as well as to anticardiolipin, was performed in the General Laboratory, HC/FM/UFG, by ELISA (Enzyme Linked Immuno Sorbent Assay).

Disease activity was assessed at inclusion in the study, using SLEDAI (Systemic Lupus Erythematosus Disease Activity Index).[19] Patients with SLEDAI ≥3 were considered active. In patients with disease activity, only anti-DNA and complement (C3 and C4) levels brought at the time of inclusion were considered.

For the determination of leptin, the ELISA technique was used, in a typical capture assay in two stages, or in "sandwich", according to the manufacturer's instructions (DBC – Diagnostics Biochem Canada). The assay sensitivity was 100 ng/mL. The level of adiponectin was also obtained by ELISA in a quantitative sandwich, according to the manufacturer's protocol (MBL International Corp., Woburn, MA, USA), and the sensitivity of the assay was 100 pg/mL, with a mean recovery of 90–105% of adiponectin.

Statistical analysis

All statistical analysis were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) for Windows, version 18. Student's *t*-test was used for independent samples; equivalent variances were defined by Levene's *F*-test. The verification of the normality of the distribution was done by Kolgomorov and Smirnov test. The Mann–Whitney test was used for quantitative variables that were not normally distributed. Correlations were calculated by Pearson correlation. Categorical variables were analyzed by the chi-squared test (a measure of association). For all statistical evaluations, $p<0.05$ was considered statistically significant.

Results

There was no statistical difference between the mean age of SLE patients and controls (33.4 ± 9.4 years vs. 32.5 ± 10.5 years, $p=0.670$). The body mass index was higher in SLE patients compared to controls (23.8 ± 3.5 kg/m^2 vs. 21.8 ± 2.5 kg/m^2, $p=0.008$). The metabolic evaluation between groups showed no difference in levels of total and LDL cholesterol, but there was a difference in blood glucose levels, HDL and triglycerides (Table 1).

Table 2 – Characteristics of patients with SLE ($n=52$), according to the disease activity.

	Active SLE ($n=21$)	Inactive SLE ($n=31$)	p
Age, years*	33.4 (±9.9)	33.6 (±9.1)	0.861[a]
BMI, kg/m^2 *	23.7 (±3.5)	24.0 (±3.6)	0.760[a]
Disease duration, years*	6.0 (±6.6)	9.0 (±6.4)	0.110[a]
ESR, mm/L^2 h*	64.7 (±35.4)	31.8 (±21.6)	<0.001[a]
ANA-positive, %	90.5%	93.5%	0.170[b]
Anti-ENA, %	85.7%	61.3%	0.056[b]
Anti-DNA, %	52.4%	35.5%	0.223[b]
LA, %	19%	9.7%	0.331[b]
aCL, %	14.3%	9.7%	0.610[b]
SLEDAI*	7.42 (±3.9)	0.20 (±0.8)	<0.001[c]

SLE, systemic lupus erythematosus; BMI, body mass index; ESR, erythrocyte sedimentation rate; ANA, antinuclear factor; Anti-ENA, anti-extractable nuclear antigen antibody; LA, lupus anticoagulant; aCL, anticardiolipin; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.
* Data presented as mean (±standard deviation).
[a] *t*-Test.
[b] Chi-squared test.
[c] Mann–Whitney test.

Table 2 presents the characteristics of SLE patients with active disease ($n=21$). The mean age in the active SLE group was similar to the group of patients with inactive SLE (33.4 ± 9.9 years vs. 33.6 ± 9.1 years, $p=0.861$). BMI did not differ between patients with active SLE and patients with inactive disease (24.0 ± 3.6 kg/m^2 vs. 23.7 ± 3.5 kg/m^2, $p=0.760$). Disease duration was not significantly different between the two groups (9.0 ± 6.4 years vs. 6.0 ± 6.6 years, $p=0.110$). The mean duration of disease activity was 5.6 months. With regards to autoantibodies (ANA, anti-ENA, anti-DNA, LA and aCL), there was no statistical difference between groups.

Adiponectin levels were lower in SLE patients, although there was no significant difference when compared with controls (87.5 ± 69.7 vs. 118.1 ± 70.6 μg/mL, $p=0.053$). There was also no significant difference between patients with active and inactive SLE (88.8 ± 74.4 vs. 85.5 ± 95.9 μg/mL, $p=0.866$). Leptin levels in SLE patients and controls are shown in Figs. 1 and 2. Leptin levels were significantly higher in SLE patients compared to controls (20.7 ± 17.1 vs. 8.0 ± 5.0 ng/mL, $p<0.001$). There was no significant difference in leptin levels between patients with active and inactive SLE (21.1 ± 19.8 vs. 20.4 ± 15.3 ng/mL, $p=0.874$).

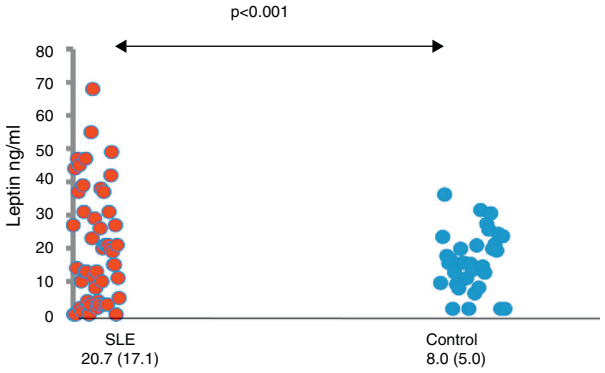

Figure 1 – Serum leptin levels (DP) in SLE patients and controls.

The correlation between leptin levels and lipid profile, blood glucose and BMI showed a positive association between leptin levels and HDL ($r = 0.34$, $p = 0.014$) and between leptin levels and BMI ($r = 0.34$, $p = 0.014$) only in SLE patients. Adiponectin levels were not correlated to the variables studied in SLE patients.

There was no significant correlation of leptin with ESR ($r = -0.062$, $p = 0.666$) or SLEDAI ($r = -0.053$, $p = 0.710$), and there was also no correlation of adiponectin with these variables (ESR, $r = 0.047$; $p = 0.743$ and SLEDAI, $r = 0.169$, $p = 0.230$).

No association of adiponectin with autoantibodies and clinical features of SLE was observed (Table 3). However, a significant association between low levels of leptin and positivity for aCL and LA was observed, as well as a significant association between high levels of leptin and the presence of renal involvement (Table 4).

Discussion

Leptin is a proinflammatory cytokine that appears to contribute to systemic inflammation in autoimmune rheumatic diseases, including SLE.[4,5] In the present study, leptin levels were significantly higher when compared with the control group, a finding that was also observed in several studies.[11–13,20–23]

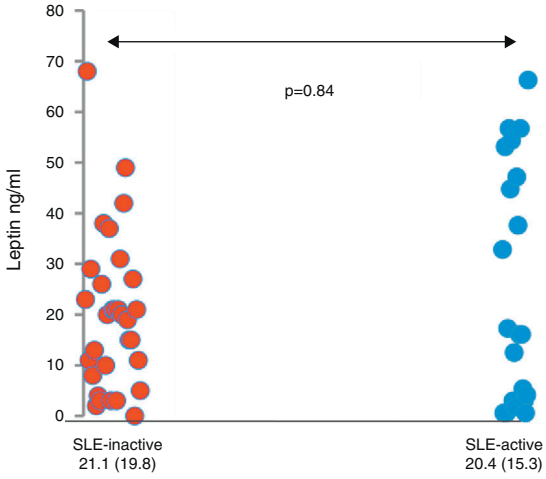

Figure 2 – Serum leptin levels (DP) in inactive and active SLE patients.

However, Wislowska et al.[24] found no difference in serum leptin levels between SLE patients and controls, while De Sanctis et al.[25] observed a significantly lower level of leptin in patients with SLE.

In our study, no significant differences in adiponectin levels between patients and controls was observed, although there was a trend toward lower levels of adiponectin in SLE patients, which was similar to the results found by Vadacca et al.[21,22] and McMahon et al.[23]

Different results were found by Sada et al.[12] Chung et al.[20] and De Sanctis et al.,[25] who observed a significant increase in adiponectin levels in patients with SLE. As adiponectin plays an anti-inflammatory, anti-atherogenic and anti-diabetic role,[14] those studies that found a higher level of adiponectin sought to justify this finding as a compensatory effect.[20,26]

One possible explanation for the different activities of adiponectin is that low molecular weight adiponectin has anti-inflammatory activity, whereas high molecular weight adiponectin has proinflammatory action, the latter being most commonly found in plasma.[14,27]

In the present study, there was a positive association between leptin and BMI in patients with SLE, but not in the control group. The same was observed by Chung et al.[20] We observed an association of leptin levels with HDL-cholesterol but not with LDL-cholesterol and triglycerides, as found by Chung et al.[20]

Regarding adiponectin, there was no correlation with any of the variables studied, although Chung et al.[20] have found a negative association of adiponectin with BMI and a positive association with HDL-cholesterol.

In this study, there was no statistical correlation between the levels of leptin and adiponectin with disease activity, measured by SLEDAI and ESR. The lack of relationship between disease activity and leptin was also observed in other studies.[11,20,24,25,28]

However, in studies conducted by Vadacca et al.,[21,22] the authors observed a correlation between leptin levels and activity indices (SLEDAI and ECLAM) in SLE, but no correlation whatsoever of these indices with adiponectin. Although leptin levels are higher in patients with SLE, these do not appear to be associated with disease activity and, therefore, would not be a marker of disease activity.

Most studies[11–13,20,23–25] include patients with low disease activity, as those with high activity are generally taking high doses of corticosteroids and, thus, are excluded. The relation of leptin in patients with SLE activity may be further clarified by studies involving patients with higher SLEDAI and without prior treatment.

In this study, there was no association between ANA, anti-ENA and anti-DNA autoantibodies with levels of leptin and adiponectin, but there was an association between low levels of leptin and the presence of LA and aCL. None of the patients included in the study presented antiphospholipid syndrome. In our literature survey, we did not find studies presenting a correlation between the presence of antiphospholipid antibodies and leptin in SLE patients. Only Garcia-Gonzalez et al.[11] evaluated the presence of anti-DNA and leptin levels, and found no correlation.

In this study, adiponectin levels were not correlated with any clinical manifestation, but high levels of leptin correlated

Table 3 – Association of adiponectin levels with the presence of autoantibodies and clinical manifestations in 52 patients with systemic lupus erythematosus.

Variables (*n*)	Presentation (*n*)	Adiponectin		*p*
		Normal (<11 μg/mL)	High (≥11 μg/mL)	
ANA (52)	Positive (47)	13	34	0.136
	Negative (5)	3	2	
Anti-Ro (49)	Positive (22)	5	17	0.280
	Negative (27)	10	17	
Anti-La (49)	Positive (7)	1	6	0.310
	Negative (42)	14	28	
Anti-Sm (49)	Positive (20)	7	13	0.580
	Negative (29)	8	21	
Anti-RNP (50)	Positive (25)	6	19	0.355
	Negative (25)	9	16	
Anti-DNA (45)	Positive (22)	6	16	0.815
	Negative (23)	7	16	
aCL (37)	Positive (6)	2	4	0.959
	Negative (31)	10	21	
LA (41)	Positive (6)	2	4	0.926
	Negative (35)	11	24	
Clinical manifestation (21)	Renal (15)	5	10	0.472
	CNS (2)	0	2	
	Cut/art (4)	2	2	

ANA, antinuclear antibody; Anti-Ro, anti-SSA; Anti-La, anti-SSB; Anti-Sm, anti-Smith; Anti-RNP, anti-U1 ribonucleoprotein; Anti-DNA, anti-deoxyribonucleic acid; aCL, anticardiolipin; LA, lupus anticoagulant; CNS, central nervous system; Cut/art, cutaneous and articular. Chi-squared test of Pearson.

with renal involvement. Wislowska et al.[24] showed a lower level of leptin in patients with arthritis and CNS involvement compared to patients without such manifestations. However, Kim et al.[13] found no correlation between leptin levels with clinical manifestations. Also, no studies correlating renal involvement and leptin levels were found.

Wang et al.[29] demonstrated that the signaling pathway of Jak/STAT plays an important role in the progression of nephritis in mice models. Considering that this signaling pathway is activated by leptin, maybe it could be the explanation of the correlation of renal disease and leptin.

Table 4 – Association of leptin levels with the presence of autoantibodies and clinical manifestations in 52 patients with systemic lupus erythematosus.

Variables (*n*)	Presentation (*n*)	Leptin			*p*
		Low (<3.7 ng/mL)	Normal (3.7–11.1 ng/mL)	High (>11.1 ng/mL)	
ANA (52)	Positive (47)	11	8	28	0.200
	Negative (5)	0	0	5	
Anti-Ro (49)	Positive (22)	5	1	16	0.210
	Negative (27)	4	6	17	
Anti-La (49)	Positive (7)	1	1	5	0.830
	Negative (42)	8	7	27	
Anti-Sm (49)	Positive (20)	5	3	12	0.394
	Negative (29)	3	5	21	
Anti-RNP (50)	Positive (25)	6	3	16	0.465
	Negative (25)	3	5	17	
Anti-DNA (45)	Positive (22)	5	6	11	0.120
	Negative (23)	3	2	18	
aCL (37)	Positive (6)	4	0	2	0.025
	Negative (31)	5	8	18	
LA (41)	Positive (6)	4	2	0	0.003
	Negative (35)	5	5	25	
Clinical manifestation (21)	Renal (15)	4	0	11	<0.001
	CNS (2)	0	2	0	
	Cut/art (4)	3	0	1	

ANA, antinuclear antibody; Anti-Ro, anti-SSA; Anti-La, anti-SS B; Anti-Sm, anti-Smith; Anti-RNP, anti-U1 ribonucleoprotein; Anti-DNA, anti-deoxyribonucleic acid; aCL, anticardiolipin; LA, lupus anticoagulant; CNS, central nervous system; Cut/art, cutaneous and articular. Chi-squared test of Pearson.

None of the patients in this study showed impaired renal function, although higher levels of leptin in patients with chronic kidney disease were described in the literature.[30] This study did not evaluate the urinary level of leptin, and more studies are needed to determine whether higher leptin levels may be a marker of renal activity.

Currently, advances in research related to SLE show that the adipokines may represent an important group for the discovery of cytokines that help to understand the pathophysiology of this disease and that can also serve as a serologic marker, assisting in the identification of patients at risk of developing severe forms or being a predictor of disease activity.

In conclusion, leptin levels are higher in patients with SLE and there was a trend to lower adiponectin levels. High leptin levels do not seem to reflect the activity of the disease. Renal involvement was the only clinical manifestation that was associated with increased leptin levels, and there was an inverse association of serum levels of leptin with the presence of lupus anticoagulant and anticardiolipin. The role of leptin in SLE needs to be better clarified, and studies including larger numbers of patients, different stages of disease and different clinical presentations are required.

Conflicts of interest

The authors declare no conflicts of interest.

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